REMARKS

The specification has been amended to recite that the patent or application file includes a color photograph, as required by the Examiner. The address of the American Type Culture Collection has been corrected at page 240, as required by the Examiner. No other references to the American Type Culture Collection were found that required correction. No new matter is introduced by way of these amendments

Claims 1-7, 19-22, 26-29 and 31-36 are pending in the application, with Claims 2-4, 6-7, 20, 22, and 27 being withdrawn from consideration. Accordingly, Claims 1, 5, 19, 2, 26, 28-29, and 31-36 are under consideration in the application.

Claims 1, 5, 19, 21, 26, 28-29 and 31-36 stand rejected under 35 U.S.C. §112, first paragraph as allegedly not enabled; Claims 1, 5, 19, 21 and 31-35 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly obvious over Claims 1, 5, 13, 15-16, 18, 19, 21, 24, 26, 29, and 32-37 of copending Application No. 09/489,394; and Claims 1, 5, 19, 21 and 31-35 are also alleged to be not patentably distinct from Claims 1, 5, 13, 15-16, 18, 19, 21, 24, 26, 29, and 32-37 of copending Application Serial No. 09/489,394.

The Rejections under 35 U.S.C. §112, first paragraph

Claims 1, 5, 19, 21, 26, 8-29 and 31-36 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully traverse the rejections of Claims 1, 5, 19, 21, 26, 8-29 and 31-36 under 35 U.S.C. §112, first paragraph.

The Examiner states: "Thus the Examiner maintains that the specification does not appear to provide sufficient guidance as to how only a single PEG, as currently recited, may be covalently coupled to the recited Fab' fragment having two reactive cysteines." Applicants respectfully disagree, and submit that the specification provides sufficient guidance to enable one of ordinary skill in the art to make and use the invention. Applicants respectfully note that the present claims are directed to a

conjugate of a single antibody fragment covalently attached to a single PEG molecule, irrespective of how the conjugate is made or purified.

The specification teaches how to prepare a conjugate of a single antibody fragment covalently attached to a single PEG molecule by methods including protecting a cysteine and then deprotecting it, by PEGylating a population of antibody fragments and then separating out or purifying those antibody fragments covalently attached to a single PEG molecule from other antibody fragments that may be attached to multiple PEG molecules, and by other means. Applicants respectfully submit that the teaching of the specification enables one of ordinary skill in the art to practice the invention.

As mentioned by the Examiner, an example of one way to obtain antibody fragments having a single PEG residue are described in Example T. For example, methods of protecting and deprotecting sulfur groups are described in Example T at pages 226-229.

Applicants note that the specification additionally provides further guidance and direction describing methods for producing and selecting a desired amount of polymer derivatization of antibodies. Applicants respectfully submit that the specification teaches one of ordinary skill in the art how to make antibody conjugates having a single PEG residue, including methods for preparing PEG-antibody conjugates in which more than 50% of the conjugates have only a single PEG residue, and for purifying populations of such conjugates.

For example, the specification at pages 77 to 78 states "The degree of substitution with such a polymer will vary upon the number of reactive sites on the antibody fragment, the molecular weight, hydrophilicity and other characteristics of the polymer, and the particular antibody fragment derivatization sites chosen. ... The desired amount of derivatization is easily achieved by using an experimental matrix in which the time, temperature and other reaction conditions are varied to change the degree of substitution, after which the level of polymer substitution of the conjugates is determined by size exclusion chromatography or other means known in the art." (from the paragraph at page 77, line 23 to page 78 line 3). Further guidance is provided in the

specification, for example, on page 78-79, where methods useful in preparing singly and multiply conjugated antibodies are described.

In particular, the specification describes methods for providing a population of derivatized antibodies conjugated with a desired number of PEG derivatives, including resolving different species such as those having only one PEG residue (see, *e.g.,* page 79, line 20). See, for example, page 79, lines 8-25, particularly at page 79, lines 18-21. At page 79, lines 13-16, the specification states:

> "The conjugates of this invention are separated from the unreacted starting materials by gel filtration of ion exchange HPLC. Heterologous species of conjugates are purified from one another in the same fashion. [new paragraph] The conjugates may also be purified by ion-exchange chromatography. ... Thus, high resolution ion exchange chromatography can be used to separate the free and conjugated proteins, and to resolve species with different levels of PEGylation. In fact, the resolution of different species (*e.g.,* containing one or two PEG residues) is also possible due to the difference in the ionic properties of the unreacted amino acids. In one embodiment, species with difference (sic) levels of PEGylation are resolved according to the methods described in WO 96/34015 (International Application No. PCT/US96/05550 published October 31, 1996)." (emphasis added)

In addition, other methods are also described that may be used to separate antibody conjugates having a single PEG residue from other conjugates. Example U (page 221, line 26 to page 226) teaches preferred methods for preparing antibody conjugates. For example, the specification notes that reaction at pH 8 is preferable to reaction at pH 7 (page 222, lines 2-4 and 9-10), and provides other instruction as to methods for practicing the invention (*e.g.,* pages 222-225). These methods "generated a mixture of 50% singly-labeled anti-IL8" (page 224, lines 14-15; emphasis added) and "were the optimal conditions for obtaining the greatest recovery of the protein with only 1 PEG per antibody" (page 225, lines 3-4; emphasis added).

In addition to describing successful and preferred methods for practicing the invention, the specification further provides guidance regarding methods that have been found not to be helpful, in order to help one of ordinary skill in the art to avoid less efficient methods and to guide them in a proper direction. For example, at page 78, lines 4-25, the pros and cons of various alternative methods for covalent modification of

proteins are discussed, including methods which are not preferred (*e.g.,* lines 7-12 and 14-16), as well as, methods which are preferred (*e.g.,* lines 16-17, 21-23 and 24-25).

Thus, the specification provides detailed and explicit teaching as to methods for achieving a desired amount of derivatization and for obtaining species having the desired number of PEG residues, including species having only a single PEG residue covalently attached to a first cysteine residue in the first chain that would ordinarily form a disulfide bridge with a second cysteine residue in the first opposite chain.

A Declaration under 37 C.F.R. § 1.132 by one skilled in the art is in preparation. The Declaration by an experienced research scientist with knowledge of the level of skill in the relevant art will further support the present arguments that the claimed invention was fully enabled at the effective filing date of this application.

Applicants respectfully submit that the detailed and explicit guidance provided by the specification provides sufficient teaching that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, Applicants believe the rejections to claims 1, 5, 19, 21, 26, 8-29 and 31-36 under 35 U.S.C. §112, first paragraph to be overcome.

The Provisional Double-Patenting Rejections

Claims 1, 5, 19, 21 and 31-35 stand rejected under the judicially created doctrine of obviousness-type double patenting over Claims 1, 5, 13, 15-16, 18, 19, 21, 24, 26, 29, and 32-37 of co-pending U.S. Patent Application Serial No 09/489,394. Applicants respectfully traverse these provisional rejections, for at least the reason that Claims 1-7, 9-11, 13, 15, 16, 18-24, and 26-37 of co-pending U.S. Patent Application Serial No 09/489,394 stand canceled by the Preliminary Amendment filed on January 30, 2003 in that case (photocopy enclosed). Thus, all of the claims cited in the rejection (*i.e.,* Claims 1,5, 13, 15-16, 18, 19, 21, 24, 26, 29, and 32-37) have been canceled in co-pending U.S. Patent Application Serial No. 09/489,394, so that the rejection is moot.

Moreover, as these rejections are provisional, Applicants respectfully await an indication of allowable subject matter in the present case, at which time a determination

of whether common subject matter has been claimed in both applications, and as to the suitability of a Terminal Disclaimer may be assessed.

The Requirement to Show Common Ownership

The Examiner has required that the assignee show that the conflicting inventions were commonly owned at the time the invention in this application was made. Applicants note that the present application, U.S. Patent Application Serial No. 09/234,182, is assigned to Genentech, Inc. The assignment was recorded with the U.S. Patent and Trademark Office on May 20, 1999 at reel/frame: 010021/0349.

U.S. Patent Application Serial No. 09/489,394 is also assigned to Genentech, Inc. The assignment was recorded with the U.S. Patent and Trademark Office on October 3, 2000 at reel/ frame: 011202/0462. Photocopies of the assignment recordation documents are enclosed.

Accordingly, the applications being commonly assigned at the time the invention was made, Applicants respectfully submit that the requirement to show that the "conflicting" inventions were commonly owned at the time the invention in this application was made has been fulfilled.

CONCLUSION

In conclusion, based on the enabling disclosure of the specification, the high level of skill and experience of one of skill in the art, and in view of the arguments presented above, Applicants respectfully submit that the specification teaches one of skill in the art how to make and use the claimed invention to the full scope of the claims without undue experimentation, and thus that the claims fully comply with the enablement requirement of 35 U.S.C. §112, first paragraph. The provisional claim rejections under the judicially-created doctrine of obviousness-type double patenting being provisional, and the common ownership of the present invention with that of U.S. Patent Application Serial No. 09/489,394. Accordingly, Applicants respectfully submit that all pending claims are in condition for allowance, and request reconsideration and allowance of all pending claims.

The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding,.

Although no fees are believed to be due at this time, please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39766-0093 A**.

Respectfully submitted,

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